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10/677,734	10/01/2003	Kevin H. Gardner	UTSD:1510-1	4912
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EXAMINER				
SWOPE, SHERIDAN				
ART UNIT		PAPER NUMBER		
1652				
NOTIFICATION DATE		DELIVERY MODE		
11/19/2008		ELECTRONIC		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary

Application No.

10/677,734

Applicant(s)

GARDNER ET AL.

Examiner

SHERIDAN SWOPE

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 September 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21 and 22 is/are pending in the application.
- 4a) Of the above claim(s) 22 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/CDC)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____
- Paper No(s)/Mail Date _____

DETAILED ACTION

Applicants' Request for Continuing Examination of September 15, 2008, in response to the BPAI decision rendered July 15, 2008, is acknowledged. It is acknowledged that Claims 21 and 22 have been amended. Claims 21 and 22 are pending. Claim 22 was previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claim 21 is hereby reexamined.

Information Disclosure Statement

It is noted that an Information Disclosure Statement has not been filed.

It is noted that, in their declarations and remarks through-out prosecution, Applicants have referred to published art that has not been cited on an Information Disclosure Statement and has not been provided to the office. Said published art is, thus, is not of record.

Specification-Objections

Objection to the specification for having two versions of the figure legends, as acknowledged by Applicants in their response of October 9, 2006, is maintained.

Objection to the specification because, on page 18 line 7, "Compound KG0721, as well as X others...", it is unclear what "X" refers to, is maintained.

Objection to the specification for having an undefined abbreviation, Dd, is maintained.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 1010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Provisional rejection of Claim 21 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1 of US Application 10/677,733, for the reasons set forth in the prior action, is maintained. Applicants state they will file a terminal disclaimer when the instant invention becomes allowable.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 21 recites a method of "changing a functional surface binding specificity of a selected PAS domain...comprising the steps of: contacting the PAS domain with a small organic compound, whereby the compound enters the hydrophobic core of the PAS domain". It is unclear whether said method comprises a method of (i) screening for ligands that, by entering the hydrophobic core, alter the PAS domain surface binding, (ii) altering the PAS domain surface binding by contacting the domain with a known ligand, which is known to enter the hydrophobic core and, thereby, alter the PAS domain surface binding, or (iii) both (i) and (ii).

It is noted that Applicants' affirmed that that the prior phrase of Claim 21, "changing a functional surface binding specificity of a selected PAS domain...comprising the steps of: introducing into the hydrophobic core of the PAS domain a foreign ligand...", encompassed both a method "to screen for ligands" as well as "practicing the method with a known [functional] ligand" (response of October 9, 2006; pg 4, para 6).

Thus, for purposes of examination herein, it is assumed that Claim 21 encompasses both (i) a method of screening for ligands that, by entering the hydrophobic core, alter the PAS domain surface binding and (ii) a method of altering PAS domain surface binding by contacting the domain with a known ligand, which is known to enter the hydrophobic core and, thereby alter the PAS domain surface binding. It is requested that Applicants respond to this rejection and clarify the meaning of a method of "changing a functional surface binding specificity of a selected PAS domain...comprising the steps of: contacting the PAS domain with a small organic compound, whereby the compound enters the hydrophobic core of the PAS domain".

Written Description

Rejection of Claim 21 under 35 U.S.C. 112, first paragraph written description, for the reasons explained in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments. As explained in the specification, suitable foreign ligands may be screened from libraries of synthetic and natural compounds. Such screening was exemplified with HIF2 α PAS-B, wherein a "lead" ligand was identified (pg 13, 18, and 31; Fig 1). The practitioner does not require any a priori structural characteristics of the recited "foreign ligand" to practice the method.

These arguments are not found, or are found, to be persuasive for the following reasons.

These are the same arguments provided in Applicants' responses of October 9, 2006 and March 19, 2007. Applicants are referred to the Offices' responses of January 5, 2007 and July 16, 2007 as to why these arguments are not found, or are found, to be persuasive.

In addition, the following reasons are provided. As explained above, for the rejection under 35 U.S.C. 112, second paragraph, Claim 21 encompasses a genus of methods for altering the HIF2 α PAS-B domain surface binding by contacting the domain with a known ligand, wherein the ligand is known to enter the hydrophobic core and, thereby, alter the PAS domain surface binding, as measured by 1H/15N-HSQC NMR. The specification discloses no such method. Moreover, the specification fails to describe any other representative species of said methods by any identifying characteristics or properties other than the functionality of being a method for affecting the surface binding of a HIF2 α PAS-B domain, as measured by 1H/15N-HSQC NMR, by introducing into the PAS-B domain hydrophobic core a foreign ligand. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

For these reasons and those explained in the prior actions, rejection of Claim 21 under 35 U.S.C. 112, first paragraph written description, is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Rejection of Claim 21 under 35 U.S.C. 103(a) as being unpatentable over Vogtherr et al, 2003 or Amezcua et al, 2002 in view of Ema et al, 1997 and further in view of Fukunaga et al, 1995, for the reasons explained in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants have filed, under 1.132, a declaration from Inventor Kevin H. Gardner providing the following arguments.

(A) At the time my laboratory published Amezcua et al, 2002, it was believed that there were two distinct and mutually-exclusive types of PAS domains: (i) those with an endogenous core cofactor which was required for folding, stability, and sensing and (ii) those without a core pocket or a core cofactor. AhR PAS2 is an example of the first type; comprising an endogenous core cofactor. However, for most PAS domains there is no evidence for such a cofactor. In fact, structurally characterized PAS domains without bound cofactors show tightly packed cores having no pre-formed cavities that would suggest a cofactor or ligand binding site (Amezcua et al., 2002; Erbel et al., 2003; Morais Cabral et al., 1998).

(B) No one had obtained structures of both members of cognate pairs of the same PAS domain, with and without ligand, suggesting that the cofactored PAS domains were unstable and did not adopt unique, well-defined conformations in their "apo" (cofactor-free) forms.

(C) NMR and crystallographic data distinguished the two types of PAS domains: PYP and AhR, of the cofactored class, have a hydrophobic core pocket containing the cofactor, while HERG and HIF2 α PAS-B, of the non-cofactored class, showed a tightly packed core. See Cusanovich et al, [2003].

(D) The sequence of HIF2 α PAS-B (Tian et al, 1997) did not indicate the presence of any such extended loops, dynamic regions or unusual flexibility as we observed with PASK PAS-A.

(E) Finally, it was known that the oxygen-dependent transcriptional regulation conferred by HIF2 α was encoded in protein regions outside the PAS-B domain (O'Rourke et al., J. Biol. Chem. 1999, 274: 2060- 2071), further lowering expectations that the PAS domains themselves bound any oxygen-sensitive ligand or cofactor.

These arguments are not found to be persuasive for the following reasons.

(A) Reply: This is essentially the same argument provided by Applicants' response of June 22, 2006. Applicants are referred to the Office' rebuttal of September 1, 2006.

In addition, the following reasons are provided. Amezcua et al teach a solution structure for the hPASK PAS-A domain, but does not teach whether or not said domain has a structure that is similar or dissimilar to the HIF2 α PAS-B domain. In fact, Amezcua et al teach that some PAS domains, containing well-packed hydrophobic cores, lacking any obvious cavities for binding of small ligands, and folding stably in a ligand-free state, are not precluded from function as sensors (pg 1358, para 4). Amezcua et al also teach that such a domain, the PASK PAS-A domain, binds organic ligands within its core (Fig 4 pg 1358, para 4). Amezcua et al further state that: "a very broad range of PAS domains, including those that do not copurify with ligands when isolated from natural sources, may serve sensor roles in vivo" (pg 1358, para 5). Therefore, Amezcua et al suggest that PAS domains having no obvious pre-formed cavities, such as the HIF2 α PAS-B domain, may still bind small molecules within their core and/or act as sensors.

As explained in the prior actions, Erbel et al, 2003 cannot be used as evidence to overcome the instant rejection because it was published after Applicants' priority date. Morais Cabral et al teach the structure of the HERG K⁺ channel PAS domain, but does not teach whether or not said domain has a ligand-binding pocket or whether its structure is similar or dissimilar to the HIF2 α PAS-B domain. Therefore, none of Amezcua et al, Erbel et al, or Morais Cabral et al provide evidence that, prior to filing, it was known that the HIF2 α PAS-B domain has, or does not have, a ligand-binding pocket.

(B) Reply: Fukunaga et al, 1995, Dolwick et al, 1993, and Henry et al, 1993 teach away from Applicants' assertion for the following reasons. Fukunaga et al teach that (i) AhR, including a variant lacking the PAS-B domain, can be expressed and processed in the absence of a ligand (pg 29271, para 7; Fig 2) and (ii) AhR is capable of dimerizing with Arnt, binding XRE, and activating a reporter gene in the absence of the dioxin ligand (Table I). Dolwick et al teach that (i) AhR can be expressed in the absence of ligand, (ii) an AhR variant lacking the PAS-B domain binds DRE and XRE (Fig 3), and (iii) rather than promoting protein folding, binding of ligand to the PAS-B domain may serve a repressive effect on AhR activity, since DRE binding was repressed in the presence of ligand (pg 8569, para 3). Henry et al teach that, in the presence of hsp90, dioxin dissociates readily from AhR (Abstract; Fig 7). Based on these results, the skilled artisan would believe that, more likely than not, AhR can be expressed, properly folded, and function in the absence of a ligand bound to the PAS-B domain (also see Fukunaga et al pg 29277, para 2).

The instant rejection is based on what was known in the art: that both AhR and HIF2 α regulate transcription via the Arnt DNA binding protein (Fukunaga et al, 1995), that AhR binds a

cofactor, and that, based on said teachings, the skilled artisan would be motivated to screen for compounds that bind to the HIF2 α PAS-B domain and alter the surface binding properties. None of Fukunaga et al, Dolwick et al, or Henry et al, teach away from this analysis. In fact, Fukunaga et al, in teaching that AhR can be functional in the cofactor-bound and un-bound state is consistent with the instant rejection.

(C) Reply: Cusanovich et al provide no information on the 3-dimensional structure or flexibility of HIF2 α . Cusanovich et al merely discloses teachings on Photoactive Yellow Protein, which they state is a 3-dimensional structural prototype for other PAS domains, including HERG (pg 4765, parag 5; Fig 6& 8).

(D) Reply: This is the same argument provided in Applicants' responses of June 22, 2006, October 9, 2006, and March 19, 2007. Applicants' are referred to the Offices' responses of September 1, 2006, January 5, 2007, and July 16, 2007. In addition, the following comments are made.

Tian et al provides no information on the 3-dimensional structure or flexibility of HIF2 α . Tian et al merely discloses the sequence, gene structure, mRNA expression pattern, binding with ARNT, and reporter gene activation for a homologous protein, endothelial PAS-1/EPAS1. The skilled artisan would not be able to deduce, from Tian et al, the 3-dimensional structure of HIF2 α or whether the PAS-B thereof binds a ligand.

(E) Reply: This is the same argument provided in Applicants' responses of June 22, 2006, October 9, 2006, and March 19, 2007. As explained in Action of September 1, 2006, pg 9:

"It is acknowledged that the art teaches that non-PAS domain mediated mechanisms can regulate the response of HIF to oxygen. However, said teachings do not provide a *prima facie* case against the PAS domain also mediating an effect of oxygen, or any other ligand, on HIF."

For these reasons and those presented in the prior actions, rejection of Claim 21 under 35 U.S.C. 103(a) as being unpatentable over Vogtherr et al, 2003 or Amezcua et al, 2002 in view of Ema et al, 1997 and further in view of Fukunaga et al, 1995 is maintained.

Applicant's amendment necessitated any new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
Primary Examiner, Art Unit 1652